Kidney International, Vol. 3 (1973), p. 55–56

Selected topics on immunological aspects of renal disease

Introduction

During the last few years, it has become apparent that immunological mechanisms are involved in the renal injury of a significant number of cases of human glomerulonephritis. The best evidence is available in systemic lupus erythematosus (SLE) and in Goodpasture's disease where two quite different immunological processes have been implicated, circulating immune complexes in the case of SLE, and anti-glomerular basement membrane (GBM) antibodies in the case of Goodpasture's disease. However, increasing information has been forthcoming recently for similar immunological mechanisms behind a number of other types of glomerulonephritis.

The definition of these two immunopathogenic mechanisms in glomerular disease was first achieved in experimental models. Acute and later chronic serum sickness served as the prototypes of circulating immune complex glomerulonephritis in which antigen-antibody complexes immunologically unrelated to the glomerulus caused the disease. The use of labelled foreign serum antigens in these studies permitted detection of immune complexes in the circulation and in the injured glomeruli. Heterologous nephrotoxic serum nephritis and, later on, the autoimmune form of this experimental disease provided a demonstration of the pathogenicity of antiGBM antibodies. Isotope-labelled antibodies and immunofluorescent techniques revealed the precise site of antibody binding and allowed quantitation of this desease-producing reaction. Both immune complex and antiGBM models have been used in studies of the mediators of antibody-induced injury in the glomeruli. It appears that complement (C) and polymorphonuclear leukocytes (PMN) have central roles in the mediation of this disease in most situations. However, alternate non-C and non-PMN-dependent pathways of injury can also operate with particular kinds of antibodies.

It is becoming increasingly evident that the dominant immunological mechanism involved in human renal disease is the immune complex type. However, only a few of the significant immune complexes have been identified and the above conclusion is based primarily on the character of the deposits visualized in fluorescent antibody studies in different cases. Granular deposits of Ig and complement along the glomerular basement membrane in early disease and large lumpy deposits in advanced disease appear to represent the hallmarks of immune complex injury. A high percentage of biopsy specimens from patients with SLE show such fluorescence patterns. It is also common in glomerulonephritis of unknown etiology of the membranous and membrano-proliferative types. A variety of other conditions also show such patterns including patients with poststreptococcal glomerulonephritis, malaria, infection hepatitis with Australia antigen, measles, periarteritis nodosa, drug toxicity and "mixed" cryoglobulinemia. Considerable additional information is available regarding the character of the immune complexes in SLE as well as in malaria and mixed cryoglobulinemia.

The most definitive information regarding the nature of significant immune complexes in certain of these disorders has been obtained from elution studies of isolated glomeruli obtained at autopsy. In the case of SLE, antibodies to native and single-stranded DNA have been obtained with activities per milligram of γ-globulin which is many times that found in the serum. Antibodies to thyroglobulin also have been demonstrated in a similar fashion in one case of idiopathic glomerulonephritis. Another useful procedure has been the detection of antigens in the glomerular deposits by fluorescent antisera to the antigens. This method has shown the presence of native and single-stranded DNA in the glomerular deposits of SLE and malaria antigen in the case of the nephritis in malaria. It also has been applied recently in a search for hepatitis antigens in renal deposits with occasional positive results in periarteritis nodosum. Direct identification of complexes in the serum of patients with renal disease has thus far provided only limited indirect information. Ultracentrifugal analyses show complexes in a number of conditions but these are primarily less significant types that fail to fix complement; the more important complexes appear to be removed rapidly from the circulation. Recently, somewhat more success has been achieved with sensitive procedures involving precipitation with the isolated Clq component of complement and isolated monoclonal rheumatoid factors. Determination of cryoglobulins is proving to be another useful and sensitive method; certain complexes may be just soluble at 37° C but precipitate out on standing at 4° C. Complexes involving IgM anti-γ-globulins in "mixed" cryoglobulinemia and in certain patients with SLE are particularly well detected and

studied by the cryoglobulin method. Idiotypic antisera to components of the cryoglobulin have demonstrated their presence in renal deposits.

Another approach that has proven to be of value, particularly in SLE, is the long term study of patients with determinations of both antigen and antibody on serial sera. The appearance of antibody at one time alternating with the appearance of antigen at another time represents strong presumptive evidence for the formation of immune complexes. Both native DNA and its specific antibody as well as single-stranded DNA and its specific antibody have been observed to alternate in such a fashion in a significant number of SLE cases. Any antibody can be suspected of being involved in immune complex renal disease if antigen can appear in the serum. These relationships in SLE are considered in detail in the paper of this volume by Agnello and his associates and in the paper by West and his colleagues.

Experimental work has indicated possible sources of additional antigens in immune complex nephritis of man. This type of renal disease is relatively common in animals and in the best studied instances is usually associated with chronic viral infections. In mice, infections with the various C-type oncogenic viruses, lymphochoriomeningitis virus, polyoma and lactic dehydrogenase virus all are associated with circulating virus or viral antigen-antibody complexes which are deposited in glomeruli causing glomerulonephritis. A similar situation holds for the mink with Aleutian disease and horses with infectious anemia. To date, the only viruses implicated in human immune complex nephritis are hepatitis and measles, but this would seem to be a fruitful area for future investigation. A second possible source of antigens is from the host's own constituents. Experimentally it has been shown that antigens from the brush border of proximal renal tubules can serve as autoantigens in this form of disease. Certainly other potential autoantigens are worthy of careful scrutiny. In this regard it is not yet certain whether the nuclear antigens involved in lupus nephritis are hostderived autoantigens or from some as yet unidentified infectious agent. Studies of the lupus-like nephritis of New Zealand mice may provide a lead to the answer of this question.

The other major immune mechanism of renal injury in humans, that produced by antiGBM antibodies, has been well delineated in Goodpasture's syndrome and occasionally in glomerulonephritis without associated pulmonary disease. More than sixty of these cases have now been studied by immunological methods and it is clear that virtually all show a fine linear pattern of fluorescence along the basement membrane following staining with anti-Ig antisera. Elution studies on autopsy kidneys have demonstrated the presence of antiGBM antibodies which fix to these membranes in normal kidneys. In Goodpasture's syndrome these antibodies also fix to the alveolar membranes of normal lungs. Eluates of pulmonary tissues from these patients also have been shown to fix to normal GBM. Severe nephritis has been produced in subhuman primates by the injection of these human kidney eluates. The topic of antiGBM antibodies in human glomerulonephritis is discussed in detail in the paper by Wilson and Dixon.

While the target antigen in this disease is clearly in the GBM, the source of the antigen that originally stimulates the antibody response is not known. No environmental antigen has been identified which can be implicated in this disease. Experimental work has shown that endogenous basement membrane antigens, presumably catabolic products present in normal serum and urine, can upon injection into the animal from which they were derived stimulate an antiGBM response and glomerulonephritis. If these potential autoantigens are involved in the etiology of this disease there must be other contributing factors which enhance their antigenicity and which are not as yet recognized.

In the case of poststreptococcal glomerulonephritis, the exact mechanism of renal injury remains uncertain. Some evidence has been obtained for deposition of immune complexes but other mechanisms remain under consideration. This topic is well reviewed in the manusript by Zabriskie and his colleagues. Also, in the case of the idiopathic nephrotic syndrome, the mechanism of renal injury is undetermined. Evidence for the participation of either of the two main immunological processes remains scanty. This and various other specific types of glomerulonephritis are discussed in the manuscript by Michael and his associates.

Frank J. Dixon
La Jolla, California

Henry G. Kunkel
New York, New York

Reprint requests to Dr. H. G. Kunkel, The Rockefeller University, New York, N. Y. 10021, U.S.A.